REMARKS

Claims 1-49 are pending in this application, and claims 20-49 are withdrawn from consideration, as directed to non-elected subject matter in response to the November 1, 2005 requirement for restriction.

Independent claim 1 has been amended to recite a purified, large-scale preparation comprising at least 200 grams of tissue factor pathway inhibitor (TFPI) or TFPI analog. Independent claims 10 and 19 have been similarly amended. New claims 50-54 depend from claim 1 and recite that the large-scale preparation comprises TFPI or TFPI analog in amounts of 200 grams-2.4 kg (claim 50), 200-300 grams (claim 51), 400-600 grams (claim 52), 600-900 grams (claim 53), and 800-1200 grams (claim 54). Support for these claim amendments and new claims is found on page 8, paragraph [30] of the specification.

The amendments add no new matter.

The Rejections of Claims 1-19 under 35 U.S.C. § 102

Claims 1-19 are rejected as being anticipated by Diaz-Collier *et al.*, EPO publication EP 0 559 632 A1 ("Diaz-Collier"). Applicants respectfully traverse these rejections insofar as they apply to claims 1-19 as now amended, as well as new claims 50-54.

As an initial matter, claim 1 is directed to TFPI or TFPI analog preparations having less than about 12% of *all* the recited modified species, *combined* (*i.e.*, less than about 12% of the TFPI or TFPI analog molecules are oxidized, carbamylated, deamidated, cysteine adduct, aggregated, or misfolded species). This claim scope is apparent from the specification, for example, on page 8, paragraph [29]:

> The purification method is capable of producing preparations of TFPI or TFPI analog molecules in which less than about 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0.5% of the preparation consists of "modified species." "Modified species" are oxidized, carbamylated, deamidated, acetylated, aggregated, or misfolded TFPI or TFPI analogs.

Applicants therefore respectfully submit that the Office Action is incorrect in implying, at the bottom of page 2, that "a TFPI preparation with less than 12% oxidized species [necessarily] meets the limitations of the claims." The pending claims do not read on all compositions having less than about 12% of *any one* type of modified species. It is true that a preparation with less than 12% oxidized species *and* less than about 12% *total* oxidized, carbamylated, deamidated, cysteine adduct, aggregated, or misfolded species meets the limitations of the claims. However, a preparation with, for example, only 10% oxidized species but also 8% aggregated species (18% total modified species) *does not* meet the limitations of the claims.

The Invention

Independent claims 1, 10, and 19 (and dependent claims 2-9 and 11-18) are directed to purified preparations and pharmaceutical compositions comprising tissue factor pathway inhibitor (TFPI) or a TFPI analog. Less than about 12% of the TFPI or TFPI analog molecules are modified species, which include oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and misfolded species. In addition to these properties, independent claim 19 recites a pharmaceutical formulation comprising 20 mM sodium citrate, 300 mM L-arginine, and 5 mM methionine at pH 5.5. To advance prosecution, independent claim 1 has been amended to recite a purified, large-scale preparation comprising at least 200 grams of TFPI or TFPI analog. Independent claims 10 and 19 have been similarly amended.

Applicants' invention is therefore directed to compositions containing highly purified TFPI and TFPI analogs. Specification, Abstract. These compositions are particularly "large-scale preparations of purified TFPI or TFPI analog" (*e.g.*, having at least a 200 gram quantity of the purified protein). See page 8, paragraph [30]. Applicants describe, for example, a commercial scale preparation in which "[t]he amount of TFPI or TFPI analog in the refolding step is 20,000 g." See page 28, paragraph [94]

The ability to manufacture the claimed, highly purified TFPI and TFPI analog preparations on a large scale is a result of Applicants' discovery of a defined sequence of chromatography and other operations, following the refolding of TFPI or TFPI analogs expressed in *E. coli*. In particular, after refolding, TFPI or TFPI analogs are purified by (i) SP-Sepharose fast flow (FF) chromatography, (ii) a first concentration/diafiltration step, (iii) Q-Sepharose high performance (HP) chromatography, (iv) butyl hydrophobic interaction chromatography (HIC), (v) SP-Sepharose high performance (HP) chromatography, and (vi) a second concentration/diafiltration step. Specification, paragraph [62].

The Disclosure of Diaz-Collier

Diaz-Collier discloses a method capable of producing active TFPI from *E. coli* expression systems, using various *pre-refolding* purification steps. However, Diaz-Collier discloses only one post-refolding purification step, namely cation exchange chromatography. See step (4) of embodiments A and B, page 2, lines 42 and 48. There is no teaching or suggestion in Diaz-Collier that the disclosed method is applicable for producing compositions comprising TFPI or a TFPI analog in a large-scale quantity of at least 200 grams, with the claimed level of purity.

In fact, in Diaz-Collier's "larger scale" preparation, only 500 mg of TFPI protein is purified by cation exchange chromatography (*i.e.*, the final process step following TFPI refolding). See page 11, lines 21-22. This 500 mg scale preparation is consistent with Diaz-Collier's publication of the same method in THROMBOSIS AND HAEMOSTASIS, 71(3): 339-46 (1994). In the final paragraph on page 345 of this publication, the authors remark that "the present *E. coli* system is capable of generating about 300 mg of highly active TFPI from a 10-liter fermentation culture." Nowhere does Diaz-Collier suggest that commercial quantities of at

least 200 grams (*i.e.*, about 400-fold greater protein amounts, compared to the disclosed "larger scale" preparation) could be produced.

Patentability of Amended Claims 1-19 over Diaz-Collier

In contrast to the disclosure of Diaz-Collier, Applicants have discovered a particular sequence of operations *after refolding* (namely SP-Sepharose fast flow (FF) chromatography, a first concentration/diafiltration step, Q-Sepharose high performance (HP) chromatography, butyl hydrophobic interaction chromatography (HIC), SP-Sepharose high performance (HP) chromatography, and a second concentration/diafiltration step) that allows for the preparation of compositions containing highly purified TFPI and TFPI analogs (*i.e.*, having less than about 12% of modified species, as recited) in commercial scale quantities (*i.e.*, greater than 200 grams, as recited). Applicants' method was developed as a result of extensive research to provide commercial-scale pharmaceutical compositions comprising TFPI or TFPI analogs which would meet applicable FDA standards for purity in Phase III clinical trials. These purity standards for commercial-scale preparations of TFPI and TFPI analogs were not achieved during attempts to scale up prior art methods, such as the methods disclosed in Diaz-Collier, for commercial production purposes.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Diaz-Collier does not meet the legal standard for anticipation, at least because this reference does not describe or suggest a large-scale, purified preparation or pharmaceutical composition comprising at least 200 grams of TFPI or a TFPI analog, as recited in claims 1-19. New claims 50-54 depend from claim 1 and are therefore patentable for at least the same reasons that claim 1 is patentable.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

The Rejection of Claim 19 under 35 U.S.C. § 103

Claim 19 is rejected as obvious over Diaz-Collier in view of Chen *et al.*, U.S. Patent No. 6,525,102 ("Chen"). Applicants respectfully traverse these rejections.

Claim 19 is directed to a large-scale pharmaceutical composition comprising ala-TFPI. Less than about 12% of the ala-TFPI molecules are modified species. Modified species have one or more of the following modifications: oxidation, carbamylation, deamidation, cysteine adducts, aggregation, and misfolding. The pharmaceutical formulation comprises 20 mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, at pH 5.5. Claim 19 has been amended to recite that the pharmaceutical formulation comprises at least 200 grams of ala-TFPI.

A *prima facie* case of obviousness requires that the prior art reference (or references when combined) teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974) (emphasis added). For the same reasons given above with respect to the rejections under 35 U.S.C. § 102, Diaz-Collier neither describes nor suggests a large-scale pharmaceutical formulation comprising at least 200 grams of ala-TFPI as recited in claim 19. Chen fails to cure this deficiency of Diaz-Collier.

In contrast to the disclosures of Diaz-Collier and Chen, Applicants have discovered a "purification method [that] produces preparations of TFPI or TFPI analog molecules that contain fewer modified TFPI or TFPI analog species than previous purification methods . . . The purification of TFPI or TFPI analog is largely achieved after the folding step by a sequence of chromatography operations." Specification, paragraphs [63] and [64]. The sequence of chromatography operations, as set forth in detail throughout Applicants' specification, is not found in the prior art. The purification method disclosed by Applicants allows for the large-scale

preparation of TFPI or TFPI analog (*e.g.*, in greater than 200 gram quantities) having the level of purity recited in claim 19.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the above amendments remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested. This response is believed to completely address all of the substantive issues raised in the Office Action dated January 24, 2007.

Please continue to direct all correspondence in this application to Novartis Vaccines and Diagnostics, Inc. (formerly Chiron Corporation), Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,
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